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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/813,977	DYNAN ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *20-26 and 30-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The Election filed 11/29/05 in response to the Office Action of 10/20/05 is acknowledged and has been entered. Applicant elected group II, claims 5-19 and 27-29, with traverse.

The traversal is on the ground(s) that Applicant alleges groups I, II, and V are distinct inventions. Upon further review, Examiner has decided to include group I with the examination of group II, however arguments for examining group V with groups I-II is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Groups I and II are drawn to DNA repair modulators which bind polypeptides, while group V is drawn to a polynucleotide vector. Products of groups I-II and group V are made by materially different methods, and are used in materially different methods which have different modes of operation, different functions, and different effects. Further, searching and examining each of these products would result in a serious burden on the examiner. Furthermore, it is noted that the literature search, particularly relevant in this art, is not coextensive and is very important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is made FINAL.

Claims 1-60 are pending.

Claims 20-26 and 30-60 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1-19 and 27-29 are currently under consideration.

Objections

The specification is objected to for improper disclosure of polypeptide sequences, as it fails to comply with the requirements of 37 CFR 1.821 through 1.825. The description of SEQ ID NO:16 in the specification and claims is not the same as the computer readable form (CFR) of the "Sequence Listing" or the paper copy of the "Sequence Listing" submitted on 3/31/04. SEQ ID NO:16 in the specification and claims has an N-terminal lysine not found in SEQ ID NO:16 of the CFR or the paper copy (see MPEP 2422). Proper correction is required.

The specification is further objected to because it contains an embedded hyperlink and/or other form of browser-executable code (page 21, line 28). Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 4, the phrase "less than about" renders the claim indefinite because it is not clear from the claims or the specification what is meant by "less than about". This renders the claim indefinite because the term "less than about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Given the above reasons, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6-19, and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of **DNA repair modulators**, a genus of **single chain antibodies which inhibit DNA repair**, and a genus of **prodrugs**. However, the written

description in this case only sets forth a DNA repair modulator comprising SEQ ID NO:17 and a single chain antibody that includes complementarity determining regions (CDRs) SEQ ID NO:18-23. The specification does not disclose any other DNA repair modulator or single chain antibody which inhibits DNA repair, as broadly encompassed by the claims. Further, the specification does not provide a written description of a single prodrug. This is a **written description** rejection.

The specification teaches a "DNA repair modulator includes, but is not limited to, compositions such as polypeptides, for example antibodies; modified polypeptides; and branched or unbranched aliphatic, cycloaliphatic, substituted aliphatic, aromatic hydrocarbons, or heterocyclic carbon-based compounds that associate with a DNA repair polypeptide, for example, DNA-PKcs" (see page 3 lines 10-14 of specification). However, the written description only reasonably conveys a DNA repair modulator comprising SEQ ID NO:17 and a DNA repair modulator that is a single chain antibody that includes complementarity determining regions (CDRs) SEQ ID NO:18-23 (see page 18 lines 14-29, in particular). The only single chain antibody described in the specification is comprised of the CDRs SEQ ID NO:18-23 (see page 18 lines 14-29, in particular). Further, the specification states the term "prodrug" refers to an agent, including nucleic acids and proteins, which is converted into a biologically active form in vivo (page 13 lines 8-9). The specification also states that a prodrug may be converted into a parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis (pare 13 lines 13-14). A description of a genus may be achieved

by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus of DNA repair modulators, a genus of single chain antibodies that inhibit DNA repair, or the genus of prodrugs. That is, the specification provides neither a representative number of examples that encompass the genus of DNA repair modulators, the genus of single chain antibodies that inhibit DNA repair, or the genus of prodrugs nor does it provide a description of structural features that are common to DNA repair modulators, single chain antibodies which inhibit DNA repair, or prodrugs. Since the disclosure fails to describe common attributes or characteristics that identify members of the genera, and because the genera are highly variant, the disclosure of a DNA repair modulator comprising SEQ ID NO:17 and a DNA repair modulator that is a

single chain antibody that includes complementarity determining regions (CDRs) SEQ ID NO:18-23 is insufficient to describe the genus of DNA repair modulators or the genus of single chain antibodies that inhibit DNA repair. Further, a lack of any examples of prodrugs is also insufficient to describe the genus of prodrugs. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genera as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of DNA repair modulators, the genus of single chain antibodies that inhibit DNA repair, or the genus of prodrugs. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only DNA repair modulators or single chain antibodies that inhibit DNA repair wherein said DNA repair modulators or said single chain antibodies that comprise SEQ ID NO:17 or that includes complementarity determining regions (CDRs) SEQ ID NO:18-23, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. 112, first paragraph. There are no prodrugs that meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Li et al (Nucleic Acids Research, 2003, 32(20):5848-5857).

The claims are drawn to DNA repair modulators comprising a portion of SEQ ID NO:17, which bind DNA-PKcs on SEQ ID NO:16, which inhibit non-homologous end-

joining and inhibit less than about 50% of DNA-PKcs enzymatic activity. The claims are further drawn to single chain antibodies that specifically bind to DNA-PKcs in a region outside the catalytic domain, wherein the single chain antibodies includes CDRs encoded by SEQ ID Nos:18-23. The claims are further drawn to pharmaceutical compositions comprising DNA repair modulators that comprise single chain antibodies that seterically inhibit SEQ ID NO:16-comprising DNA-PKcs and interact with a region of DNA-PKcs encoded by a sequence comprising SEQ ID NO:16 or a portion thereof, wherein the DNA repair modulator inhibits DNA end joining, wherein the DNA repair modulator inhibits repair of double-strand breaks, and a pharmaceutically acceptable carrier, excipient, or diluent.

Li et al teaches a DNA repair modulator comprising a single chain antibody, which was generated by using mAb 18-25 (page 5849 left column, in particular). Li et al further teaches that mAb 18-25 was previously taught by Carter et al (Mol. Cell. Biol., 1990, 10:6460-6471) (page 5849 left column of Li et al). Further, the single chain antibody taught by Li et al is identical to that described in the specification (see page 38 of the specification and compare Figures 1-4 of the specification to Figures 1-4 of Li et al, in particular). As evidenced by the specification (page 19 lines 30-31 and page 18 lines 24-29, in particular), the single chain antibody taught by Li et al (generated by the parental antibody mAb 18-25) includes the CDRs of SEQ ID Nos:18-23. It is further noted that SEQ ID NO:17 is comprised of SEQ ID Nos:18-23, thus the single chain antibody taught by Li et al comprises "at least a portion" of SEQ ID NO:17 (compare

instant SEQ ID Nos:18-23 with instant SEQ ID NO:17). Li et al further teaches that the single chain antibody binds a 25 residue sequence outside of the catalytic domain on DNA-PKcs (page 5850 right column, in particular), which, as evidenced by the specification, is SEQ ID NO:16 (page 43 lines 12-15 and page 39 lines 17-22, in particular). Further, Li et al teaches that it is presumed that the single chain antibody sterically inhibits non-homologous end-joining (page 5855 left column, in particular) and Li et al teaches that the single chain antibody inhibits less than about 50% of DNA-PKcs enzymatic activity (page 5850 right column, in particular). Further, the single chain antibody taught by Li et al inhibits repair of double strand breaks (page 5855 left column). Further, the single chain antibody taught by Li et al was prepared in a pharmaceutically acceptable carrier, excipient, or diluent (see page 5849 left column, in particular).

Claims 1-4, 6, 8, 9, 11-13, 15-17, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter et al (Mol. And Cell. Biol., 1990, 10(12):6460-6471).

The claims are drawn to compositions comprising DNA repair modulators comprising polypeptides comprising SEQ ID NO:17, or a portion thereof, that inhibit non-homologous end joining and inhibits less than about 50% of DNA-PKcs enzymatic activity by specifically interacting with DNA-PKcs on SEQ ID NO:16 outside of the DNA-PKcs catalytic domain, wherein DNA repair modulator inhibits repair of a double-strand break, and a pharmaceutically acceptable carrier, excipient, or diluent.

Carter et al teaches a monoclonal antibody, mAb 18-2, which was used in the production of the single chain antibody taught by Li et al and described in the specification (see above). As evidenced by the specification (page 19 lines 30-31 and page 18 lines 24-29, in particular), the single chain antibody taught by Li et al (generated by the parental antibody mAb 18-25) comprises the CDRs encoded by SEQ ID Nos:18-23. It is further noted that SEQ ID NO:17 is comprised of SEQ ID Nos:18-23, thus the single chain antibody taught by Li et al comprises "at least a portion" of SEQ ID NO:17 (compare instant SEQ ID Nos:18-23 with instant SEQ ID NO:17). Further, because the single chain antibody taught by Li et al was generated from the antibody taught by Carter et al, the antibody taught by Carter et al *inherently* has the same CDRs as the single chain antibody taught by Li et al. Therefore the antibody taught by Carter et al comprises "at least a portion" of SEQ ID NO:17. Further, since the single chain antibody taught by Li et al binds SEQ ID NO:16 (see above), mAb 18-2 and the single chain antibody taught by Li et al have identical CDRs, and Western blot analysis of mAb 18-2 and the single chain antibody taught by Li et al demonstrate identical binding to DNA-PKcs (as evidenced by Figure 1C of Li et al), the antibody taught by Carter et al would bind SEQ ID NO:16. Further, as evidenced by Li et al (see page 5850 right column of Li et al, in particular), the antibody taught by Carter et al inhibits non-homologous end joining. Further, as evidenced by Li et al (page 5850 right column, in particular), mAb 18-25 inhibits less than about 50% of DNA-PKcs enzymatic activity. Carter et al further teaches preparing mAb18-2 in a pharmaceutically acceptable carrier,

excipient, or diluent (page 6461 right column, in particular). Carter et al does not specifically demonstrate that mAb 18-2 inhibits double strand breaks; however, mAb 18-2 has the same CDRs as the single chain antibody taught by Li et al, binds the same regions of DNA-PKcs as the single chain antibody taught by Li et al, and, in every function tested, has been shown to performs the same functions as the single chain antibody taught by Li et al. Therefore, since the single chain antibody taught by Li et al inhibits double strand breaks (see above), absent a showing of unobvious differences, mAb 18-2 would perform the function of inhibiting double strand breaks. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not perform the same function as the claimed product. In the absence of evidence to the contrary, the burden is on Applicant to prove that this function of the claimed product is different from that taught by the prior art and to establish patentable differences. See In re Best 562F .2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2nd 1992 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Nucleic Acid Research, 2003, 31(20):5848-5857) in view of Kelley et al (US Patent 6,252,048 B1, 6/26/01) and Jang et al (Molecular Breeding, 2002, 9:81-91).

Li et al teaches as set forth above. Li et al further teaches that microinjecting a native, folded DNA repair modulator directly into the nucleus eliminates concerns over disulfide bond formation and folding in the intracellular environment (pages 5850-5851, in particular).

Li et al does not specifically teach a single chain antibody with an organelle localization signal wherein the organelle localization signal is selected from the group consisting of a nuclear localization signal and a chloroplast localization signal. However, these deficiencies are made up in the teachings of Kelley et al and Jang et al.

Kelley et al teaches a nuclear localization signal that was recombinantly added to a DNA repair protein to improve the nuclear localization of the protein (column 62 lines 25-28, in particular). Further, Jang et al teaches a protein comprised of a chloroplast localization signal (pages 82-83, in particular). Jang et al further teaches that adding a chloroplast localization signal to polynucleotide constructs expressed in plants enhances expression of the protein product (page 87-88 and Figure 5, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a single chain antibody as taught by Li et al with a nuclear localization signal as taught by Kelley et al and a chloroplast localization signal as taught by Jang et al. Further, one would have been motivated to do so because the nuclear localization signal would improve the localization of the single chain construct in a target nucleus and the chloroplast localization signal would increase the yield of the single chain antibody taught by Li et al when recombinantly produced in plants for treatment of a subject. Further, one of skill in the art would have a reasonable expectation of success in producing the claimed product since adding targeting signals is well known and conventional in the art.

Claims 1-19 and 27-29 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Carter et al (Mol. and Cell. Biol., 1990, 10(12):6460-6471) in view of

Bejcek et al (Cancer Research, 1995, 55:2346-2351), Kelley et al (US Patent 6,252,048 B1, 6/26/01), and Jang et al (Molecular Breeding, 2002, 9:81-89).

Carter et al teaches as described above.

Carter et al does not specifically teach a single chain antibody or a single chain antibody with an organelle localization signal wherein the organelle localization signal is selected from the group consisting of a nuclear localization signal and a chloroplast localization signal. However, these deficiencies are made up in the teachings of Bejcek et al, Kelley et al, and Jang et al.

Bejcek et al teaches single chain antibodies constructed from mAbs (pages 2346-2347, in particular). Bejcek et al further teaches that single chain antibodies overcome several therapeutic problems associated with intact mAbs, particularly because of the large size of the mAbs and the resultant relative inability to penetrate tissues (page 2350, in particular). Kelley et al and Jang et al teach as described above.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the mAb as taught by Carter et al to generate a single chain antibody as taught by Bejcek et al with a nuclear localization signal as taught by Kelley et al and a chloroplast localization signal as taught by Jang et al. Further, one would have been motivated to do so because a single chain antibody would overcome several therapeutic problems that would be associated with the mAb

taught by Carter et al and the nuclear localization signal would enhance the localization of the single chain antibody when recombinantly produced in plants for treatment of a subject. Further, one of skill in the art would have a reasonable expectation of success in producing the claimed product since methods of creating single chain antibodies and adding targeting signals are well known and conventional in the art.

Summary

No claim is allowed.

Discussion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER